Case Report

Case Report: Monitoring the Adequacy of Anticoagulation During CPB in Factor XII Deficiency

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ABSTRACT

Cardiopulmonary bypass was performed on a 57 year old white male with a known Factor XII deficiency. Preoperative laboratory screening revealed an abnormal activated prothrombin time of 75.8 seconds and a pre-heparinized activated clotting time (ACT) of 560 seconds. Since this ACT was prolonged, heparin administration was managed using heparin concentrations. Thrombin times, soluble fibrin monomer complexes, and D-dimers were monitored while on bypass. Additional heparin was given to maintain heparin concentration > 3.5 U/ml. Postoperatively the patient experienced no coagulopathy, no excess bleeding, and required no homologous blood product administration. The use of heparin levels by protamine titration to monitor the adequacy of anticoagulation, as monitored by D-dimers and soluble fibrin monomer complexes proved to be successful in this patient.

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INTRODUCTION

Factor XII, Hageman factor (FXII), is a single chain polypeptide that when in contact with a foreign surface becomes converted to activated FXII as part of the intrinsic coagulation pathway involving vessel endothelium and the kallikrein and kinin systems (1). While FXII is an integral portion of the coagulation cascade, it is not required for normal hemostasis to occur. FXII deficiency is detected only on routine laboratory screening tests since clinical manifestations are rarely produced (2). Patients with FXII deficiency, an autosomal recessive trait (3), do not have bleeding disorders and have successfully undergone cardiopulmonary bypass (CPB). However, safe monitoring of adequate heparin anticoagulation in these patients with prolonged ACTs is undefined.

CASE DESCRIPTION

The patient was a 57 year old white male weighing 89 kilograms with a known FXII deficiency discovered at the time of nephrolithiotomy two years previously. He had no history of bleeding complications. He had an inferior myocardial infarction six years previously and had undergone three coronary angioplasties in the last five months. Cardiac catheterization revealed three vessel coronary disease and a left ventricular ejection fraction of .41 with inferior akinesis.

Preoperative laboratory values revealed FXII activity <3%, a prolonged activated partial thromboplastin time (aPTT) and ACT (Table 1). Before, during and after CPB, a coagulation battery was monitored. Heparin was given to maintain a level of 3.5 units per milliliter (u/ml). D-dimer and soluble fibrin monomer complexes (SFMC) levels were measured to detect subclinical thrombosis (Table 1). A thrombelastograph[a] (TEG) tracing was obtained before and after bypass. The pre-bypass TEG was normal, and except an expected prolongation of the R and K with a decreased alpha angle on the postoperative study, no unusual findings occurred.

Heparin concentrations were measured in the operating room using a commercially available system that does heparin assays using heparin/protamine titration[b]. The advantage of this device was the decreased time to obtain results (several minutes compared to half an hour for average laboratory analysis). This was especially important in this case since low heparin concentrations required the immediate administration of additional heparin. When the heparin concentration was below 3.5 u/ml, the additional heparin dose was calculated based upon the estimated patient blood volume and the desired change in the heparin concentration in the blood.

After the heparin loading dose (300 u/kg), ACTs remained above 1000 seconds throughout the case (automated[c] and hand-tilt methods(4)). SFMC remained negative and D-dimers increased slightly from 0.5 to 1-2 μg/ml. This is normally seen with the progression of bypass even with adequate heparinization (5). A four vessel coronary bypass using moderate hypothermia and blood cardioplegia was performed. Protamine was administered in a 1:1 heparin-to-protamine ratio. Autologous platelet rich plasma that had been collected pre-heparinization was infused post-protamine injection.

The postoperative course was uneventful, hemostasis was easily obtained post-bypass, total chest tube output was 885 milliliters, no homologous blood products were given, and the patient was discharged home on postoperative day six with a hematocrit of 33.2% and a platelet count of 383 k/mm^3.

DISCUSSION

Since Bull's heparin dose-response work in 1975 (6), ACTs have been used to monitor the adequacy of anticoagulation during CPB (>480 seconds) (7) and reversal of heparin after protamine administration. A survey done in 1983 revealed that 97% of open heart teams monitored coagulation status. The heparin assay was used by 29% of those reporting and 68% used ACTs (8). Although some perfusionists utilize heparin assays to manage anticoagulation during CPB, a literature search revealed that the adequate heparin concentration for CPB has not been determined; however, 3-4 u/ml seems to be a frequently employed lower limit. Optimal heparin activity is patient specific. It is the patient's response to the heparin that determines whether anticoagulation is adequate; therefore, defining a minimal heparin concentration adequate for bypass for a group of patients may not be possible. Normal patients usually respond to a heparin loading dose of 300 u/kg which results in a heparin concentration of approximately 3.5 u/mL and an ACT adequate for CPB (9). This patient presented an unusual situation since the pre-heparinization ACT was prolonged at 560 seconds. The patient was not expected to be heparin resistant because the pre-heparinization ATIII level was normal (88%); therefore, the use of heparin levels by protamine titration was used to monitor adequacy of anticoagulation. We also measured the presence or absence of SFMC and D-dimer formation as more specific markers of fibrin formation. The use of heparin levels by protamine titration, monitored by D-dimer and SFMC levels, to monitor adequacy of anticoagulation proved to be successful in our patient as illustrated in Table 1.

A few papers have been published regarding CPB in patients with FXII deficiency (10-12), but none have addressed heparin management or made recommendations for heparin dosing. When the ACT is ineffective for monitoring anticoagulation, such as in FXII deficiency, we recommend monitoring heparin levels for administration of heparin and monitoring D-dimer and SFMC levels to detect subclinical clotting while on cardiopulmonary bypass.

a Haemoscope Corp., Morton Grove, IL 60053
b Medtronic HemoTec, Inc., Englewood, CO 80112
c International Technidyne Corp., Edison, NJ 08820

Table 1
Patient laboratory values. ACT= activated clotting time, aPTT= activated partial thromboplastin time, AT III= antithrombin III, BT= bleeding time, HCT= hematocrit, [heparin]= heparin concentration, Plt count= platelet count, PT= prothrombin time, TT= thrombin time, *= data not obtained at this time.

TEST [normal]	BASELINE	5'POST HEPARIN	ON CPB	30' ON CPB	90' ON CPB	POST-PROTAMINE	POST-OP
PT (sec) [11.1-12.5]	11.9	*	28.5	30.1	32.3	15.4	13.9
aPTT (sec) [24.4-36.5]	75.8	*	>100	>100	>100	>100	>100
TT (sec) [20.0-24.0]	21.8	>120	>120	>120	>120	19.9	22.1
BT (min) [1.5-8.0]	4.00	*	*	*	*	*	*
D-dimer (µg/mL) [<0.5]	<0.5	*	<0.5	1-2	1-2	*	*
AT III (%) [84-123]	88	77	46	*	53	*	*
ACT (sec) [90-110;>480]	560	>1000	>1000	>1000	>1000	327	*
[heparin] [>3.5U/ml]	0.0	4.1	2.7	3.4	2.7	0.0	*
Plt Count (k/cumm) [140-440]	149	*	*	*	*	83	127
HCT (%) [37-47]	43.8	30	22	23	25	30	20

*= data not obtained at this time

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